REMARKS

Status of the Claims

Claims 34-39, 41-64 were pending in the application at the time of the issuance of the Final Office Action. Of the above claims, 39, 41-43 and 51-64 are withdrawn from consideration.

Claims 65-68 were submitted in an Amendment filed March 17, 2008, not entered, and entry of the claims and arguments of March 17, 2008 is requested pursuant to the Request for Continued Examination filed herewith.

New claims 69 and 70 define the transketolase-like1 gene as represented by SEQ ID No.1 ***and*** SEQ ID No. 2 (claim 69) or as given in NCIB Accession No. X 91817 (claim 70).

Claims 52, 53, 55, 56, 59 and 60 are cancelled.

Accordingly, 34-39, 41 – 51, 54, 57 and 61-70 are pending, of which claims 34-38, 44-50 and 65-70 are under examination.

Turning to the Advisory Action, Applicant's appreciate the Examiner's pointing out that claim 34 might be interpreted as not requiring use of a probe. Accordingly, Applicants amend claim 34 to specifically recite use of a probe. Support for further amendments/clarifications of claim 34 can be found as follows:

"contacting said sample with a probe specific for a transketolase like-1 gene nucleic acid sequence" -WO page 9, lines 15-33, especially lines 18-22.

has a sequence that is at least 80% identical to a part of at least 15 consecutive nucleotides of SEQ ID NO:1 or is complementary or reverse complementary to such a part and wherein said probe hybridizes under stringent conditions to SEQ ID NO: 1 but does not hybridise to an other transketolase or transketolase like sequence - WO page .9 lines 19-22.

obtaining a normal control sample and contacting said sample with said probe specific for a transketolase like-1 gene nucleic acid sequence - WO page 9 lines 15-33, especially lines 18-22.

Dependent claims are amended for consistency with amended claim 34.

Following entry of Applicant's Amendment of March 17, 2008, Applicant takes this opportunity to respond to the points raised in the Advisory Action, referring to full paragraphing of page 2 of the Advisory Action:

¶1. According to the Examiner, a disclosure that does not adequately describe a product itself cannot adequately describe a method of detecting said product.

Applicants respectfully submit that the argument advanced by the Examiner might be correct ***if*** the invention was directed to an inventive method for detecting novel transketolase like-1 gene (TKT-L1; TKR). In such a case, the specification would have to teach the target and how to detect the target. However, the "method of detection" is not the invention presently claimed.

The present invention, however, concerns the important discovery of the link between:

(a) overexpression of transketolase like-1 gene (TKT-L1; TKR) and

(b) disorders characterized by abnormal cell proliferation.

This discovery provides a new tool for the early detection and diagnosis of disorders characterized by abnormal cell proliferation, such as cancers. The "point of novelty" of this invention that has to be adequately described in the specification is the link between over-expression and disorders (the discovery of which makes detection possible), not the previously defined and well known target gene. It is not necessary to describe in detail already well known probes for detecting the well known gene, and not any particular test which is well within the skill of those working in this art to carry out.

That which is well known need not be described in detail in the specification. As defined in the specification, human transketolase like-1 gene is given in SEQ. ID 1 and is further identified by GenBank Accession number X91817. Methods for detecting this gene are known.

In practical terms, the present invention makes it possible to detect disorders characterized by abnormal cell proliferation. This is done by detecting overexpression of transketolase like-1 gene in a biological sample from an individual to be diagnosed. This connection must be taught in the specification and precisely claimed in the claims. The Examiner should not require that the claims be narrowly limited to any precise test – if the claims were limited to a particular test then it would be easily within the skill of those working in the art to develop various methods to get around the claims, thus depriving applicants of claims of scope commensurate with the invention.

¶2. "Further, it is noted that the instant claims do not require said probes to be used when performing the claimed method."

Applicants appreciate the Examiner's pointing out that the claim is open to this interpretation. Applicants did not intend this interpretation, and file this RCE in order to clarify in claim 34 that the invention concerns an in vitro method comprising the following steps:

a. obtaining a biological test sample;

b. contacting the test sample with a probe specific for a transketolase like-1 gene nucleic acid sequence;

c. obtaining a normal control sample and contacting the normal sample with the probe;

d. detecting the level of polynucleotides that hybridized in the biological test sample;

e. detecting the level of polynucleotides that hybridized in the normal control sample;

f. comparing the detected level of hybrized polynucleotides from the biological test sample and the normal control sample; and

g. in the case that a higher level of polynucleotides is detected in said biological test sample as compared to said level of polynucleotides in said normal control sample, diagnosing that individual as having at least one of said disorders characterized by abnormal cell proliferation.

¶3. The Examiner, perhaps to support his position that the claims should be limited to SEQ ID NO:1 so as not to cover non-functional constructs, points out that arguments that variability can be expected in transketolase like-1 gene are not reflected in the claims as claims are direct to method of detecting any polynucleotide that hybridizes under stringent conditions to probes specific for transketolase like-1 gene and SEQ ID NO: 1. And, again, the Examiner points out that the claims do not require probes.

On review of the claims, Applicants note that in (presently amended) claim 34 the "target" for probe hybridizing is the transketolase like-1 gene (allowing diversity) and in addition SEQ ID NO: 1 (no diversity, SEQ ID NO: 1 does not change). Accordingly, while

there may be variance in the polynucleotides that hybridize, the characteristic target remains unchanged. Thus, Applicants withdraw the previous arguments.

In addition, Applicants

(a) amend claim 34 to more particularly characterize the probe,

(b) point out that as claimed the probes hybridize under stringent conditions with SEQ ID NO: 1, and

(c) now recite in the claim that the probes which hybridize with transketolase like-1 gene do not hybridise to an other transketolase or transketolase like sequence (for relevance and support, see below).

¶4. The Examiner continues to take the position that the claims should be limited to detecting levels of SEQ ID NO: 1. The Examiner considers that, for reasons discussed above, there is no support in the specification for methods for detecting levels of "polynucleotides that hybridize under stringent conditions to probes specific for a transketolase like-1 gene, wherein said probes hybridize to SEQ ID NO: 1 under stringent conditions".

Applicant respectfully submits that the invention concerns the important discovery of the link between:

(a) overexpression of transketolase like-1 gene (TKT-L1; TKR) and

(b) disorders characterized by abnormal cell proliferation.

Thus, to satisfy statutory requirements, the claims should precisely define the boundaries of this invention.

Applicant respectfully submits that the present claims precisely define the invention as concerning detecting, in comparison to normal levels, the levels of polynucleotides that hybridized with a probe specific for transketolase like-1 gene (TKT-L1; TKR), which probe does not detect transketolase (TKT) or other transketolase like sequences (TKT-L2), wherein an elevated level of TKT-L1 gene makes possible the diagnosis of a condition associated with abnormal cell proliferation. This connection is valuable and not disclosed in the prior art, thus is patentable.

Applicant discussed in detail in the previous Amendment where support could be found for the amendment to claim 34. Applicants point out again:

The construct claims from *Eli Lilly* are not directly comparable to the method claims of the instant invention. In *Ei Lilly,* the court found that when experiments had been directed to a construct made from a **rat** insulin DNA sequence, not all constructs comprising insulin DNA sequence of **any vertebrate** were enabled. However, the instant claims differ from the construct claims of *Eli Lilly* for at least the reason that the instant claims are method claims of measuring a level of polynucleotides drawn from a single individual, so therefore the concern of genes from different species functioning in different manners does not arise. Further, the instant claims are not directed a construct which may not function due to variation in the sequence, but rather drawn to a method of detecting transketolase like-1 genes, which could be expected to have some amount of variation in their sequence while maintaining functionality. To follow the claimed method, an expert in the field would measure the results level of polypeptides in the biological test sample that hybridize to probes specific for transkeolase like-1 gene, without necessarily ascertaining the exact sequence of the polynucleotides that hybridize to the probes.

Applicant further asserts that the claims as currently amended to recite "probes specific for a transketolase-like 1 gene" meet the written description requirement. The following passages from the specification support the amendments to claim 34:

> Nucleic acids as used in the context of the present invention may be all polynucleotides, which hybridise to probes specific for the transketolase like-1 sequences used herein under stringent conditions. *WO 03/089667 p. 7 line 30-32.*
>
> The primers according to the present invention specifically hybridise to the sequence disclosed herein or a part thereof under conditions suitably applied in the course of a nucleic acid amplification reaction but do not hybridise to an other transketolase or transketolase like sequence. *WO 03/089667 p. 9 line 30- p. 10 line 1.*
>
> Dissections of tumor biopsies can be semi quantitatively analysed for the mRNA level of human transketolase-like-1 gene[.] *WO 03/089667 p. 36 line 6.*

To require that claim 34 recite detecting levels of "polynucleotide SEQ ID NO: 1" rather than "polynucleotides that hybridize under stringent conditions to probes specific for a transketolase-like-1 gene, wherein the probes hybridize to SEQ ID: 1 under stringent

conditions," (but do not hybridise to an other transketolase or transketolase like sequences) would result in a claim unnecessarily narrow in view of the disclosure set forth in the specification.

Specifically regarding the enablement rejection, the Examiner argues that the claims as previously submitted were not drawn to detecting expression of TKTL1 specifically among the three transketolase genes, TKT, TKTL1 and TKTL2.

In response, Applicants submit that the claims are now precise.

The Examiner asserted that, as evidenced by the newly submitted teachings of Langbein et al (British Journal of Cancer 2006, 1-8), TKT, TKTL1, and TKTL2 are highly similar and would all have complements that may hybridize under stringent conditions to SEQ ID NO: 1. The Examiner further argues that detecting *underexpression* of TKTL2 would be indicative of colon cancer, whereas in the claimed method, *overexpression* of TKTL1 is indicative of cancer. The Examiner argues that due to the similarity of the TKT, TKTL1 and TKTL2 genes, the claims could not be practiced as broadly as claimed with any predictability of success.

In response, Applicant submitted the article Coy et al., "Molecular Cloning of Tissue-specific Transcripts of a Transketolase-Related Gene: Implication for the Evolution of New Vertebrate Genes." Genomics 32, 309-316, Article No. 0124 (1996). In this paper the authors demonstrate that under hybridization conditions as described in the paper, the TKTL1-cDNA-sequence probe does not hybridize with TKT-sequences or with TKTL2-sequences. Hence, at the time of filing, ***probes specific for TKTL1, as recited in claim 34, were known in the art.*** For the Examiner's reference, in the paper Coy et al., the term "TKTL1" as used in the application is referred to as "TKR", and "TKT" as used in the application is referred to as "TK".

The TKTL1-gene is expressed specifically only in certain tissues and cell types. The paper sets forth a procedure to detect the presence of TKTL-1 as follows:

> Hybridizations were carried out in hybridization buffer (0.5 M phosphate, 7% SDS, 0.2% BSA, 0.2% PEG 6000, 0.05% polyvinylpyrrolidone 360,000, 0.05% Ficoll 70,000, 0.5% dextran sulfate) on nylon membranes (Hybond- N Plus, Amersham). Nonspecifically bound probe was removed by washing at 65°C in 40 mM sodium phosphate, pH 7.2, 1% SDS for 60 min. *page 310, left col., lines 3-9.*

The results of the above procedure are shown in Fig. 1a and 1b. Due to the different sizes of the TKT, TKTL1 and TKTL2 transcripts, the three genes can be discriminated by the size of their transcripts by using, e.g., Northern blot technique represented in Fig 1a and 1b. From Fig. 1a and 1b of Coy et al., it is apparent to one of skill in the art that a small transcript of the TKTL1-gene (1350 bp) is highly expressed in the human heart. A hybridization band with a size in the range of that of the TKT-mRNA (ca. 2060 bp) or the TKTL2-mRNA (ca. 2837 bp) occurs neither in the fetal nor in the adult heart tissue. The band that occurs has a size of about ca 1350 bp. Due to the absence of the large TKTL1 transcript (2500bp) in fetal and adult heart, the cross hybridization of radio-labeled TKTL1 mRNA sequences to TKT or TKTL2 sequences can be evaluated in fetal and adult heart tissue. In fetal and adult heart mRNA a transcript of the size of the TKT or the TKTL2 gene is not being detected, demonstrating that TKTL1 mRNA sequences did not hybridize with TKT or TKTL2 mRNA sequences. Hence, in accordance with Coy et al., probes specific for TKTL1 over TKT and TKTL2 under stringent conditions were known in the art at the time of filing.

Therefore, by utilizing the probes of Coy et al. under stringent hybridization conditions, ***Coy et al. enables the skilled artisan to carry out a specific and selective hybridization with the TKTL-1-gene***, thereby excluding the occurrence of cross-hybridizations with other transketolase-mRNAs. Hence, even if the analysis of the claims of the US 4,652,525 patent from *Eli Lilly* as discussed above is applicable, one of skill in the art would have knowledge at the time of filing of protocols providing hybridizing conditions and probes specific for the genus of the transketolase-like-1 gene which do not hybridize with the TKT and TKTL2 sequences.

Applicant further notes that the passage the Examiner cites to conclude that TKT, TKTL1 and TKTL2, would hybridize to each others' complements under stringent conditions (Langbein et al., British J. of Cancer 2006, 1-8 at left column of page 3), states that "TKTL1 is one of three highly similar transketolases encoded by three separate genes." The Examiner does not point to a specific passage indicating that the three transketolase genes would hybridize to each others' complements under stringent conditions. Like the authors of Coy et al., discussed above, the authors of Langbein et al., utilized techniques that specifically discriminate between the three transketolase genes. *Langbein et al, left col. page 3.*

In view of the above remarks, Applicant respectfully submits that the claims as currently amended are fully enabled and fully supported by the written description. In view of the

foregoing remarks, Applicant respectfully requests that the Examiner withdraw the rejections under 35 U.S.C. §112.

¶5-6. The Examiner considers that Applicants argue that there are conditions under which probes specific for transketolase like-1 gene will not hybridize with TKT sequences and TKTL2 sequences, but these conditions are not specified in the claims.

Applicant respectfully points out that in the response of March 17, 2008 to Office Action of Nov. 16, 2008 on pages 9-10, especially page 10 §2 Applicant indicated that the probes as recited in the claims are specific for transketolase like-1 gene nucleic acids and are able to discriminate over TKT and TKTL2.

This comment reflects the state of the art.

See Example 2 of the present application. Example 2 shows that the (over-) expression of TKTL-1 and in comparison with (normal-)expression of TKT may simultaneously be detected with the simple PCR method. ***There is not any cross reaction!***

Example 1 involves a probe which hybridizes with sequences SEQ ID NO:1 and which specifically binds to TKTL-1-mRNA. That probe is an oligonuleotide and in consequence from Example 1 it is obvious that an oligonucleotid is a suitable probe for the specific detection of TKTL1-mRNA in the course of a hybridization.

Accordingly, Applicant has explained that the literature references relied upon by the Examiner when properly read in fact support Applicant's position, and have pointed to experimental evidence of ability to discriminate in the Examples.

Accordingly, this position of the Examiner should not be maintained.

¶7. The Examiner responds to Applicants' argument that transketolase like-1 gene, TKT and TKTL2 can be discriminated based on size by taking the position that

(a) this limitation is not recited in the claims,

(b) the claims are not limited to detecting transketolase like-1 genes, rather, detecting any polynucleotide that hybridizes under stringent conditions to probes specific for a transketolase like-1 gene, wherein said probes hybridize to SEQ ID NO: 1 under stringent conditions, and

(c) the claims do not require use of probes when performing the claimed method.

In response,

(a) Applicants was merely explaining that ability to discrimination was based on physical and chemical differences between the different types of polynucleotides. These differences need not be recited in the claims. All that is necessary is that probes are known having the ability to discriminate, and that the claim requires employment of such probes.

(b) the claims are limited, and specificity of detection was state of the art at the time the invention was made. Claim 34 recites "contacting said sample with a probe specific (i.e., discriminating to the required degree of selectivity) for a transketolase like-1 gene ... and **SEQ ID NO: 1**", and

(c) to rule out a possible ambiguity in the reading of the claim, Applicants amend the claim to require use of a probe.

¶7. Finally, the Examiner maintains the position that that transketolase like-1 gene, TKT and TKTL2 are highly similar and would hybridize with with each other's complements.

This point has been responded to an is believed overcome and thus moot. Applicant previously submitted the Coy article in which the authors demonstrated that, under hybridization conditions described in the paper, the transketolase like-1 gene probe does not hybridize with TKT-sequences or with TKTL2-sequences.

This publication provides sufficient evidence that those working in the art, desiring to detect transketolase like-1 gene and not TKT-sequences or with TKTL2-sequences, can easily accomplish this.

The Examiner attempts here to justify his position, and takes the position that "transketolase like-1" is broadly defined in the specification and so reads on variants with any amount of substitutions, additions, deletions and/or insertions (including TKT and TKTL2). This reading is contrary to the specification defining TKT-L1.

Applicant points out that the skilled artisan understands the term "transketolase-like-1 gene" without any doubts as that gene which is deposited and characterised under the same name at NCIB (see NCIB, search term"TKTL-1-gene" and/or X91817) .

Furthermore:

- The prior published paper of Mack et al. contains the term "TKTK-1-Gen" in combination with the data bank Accession No. X91817 (table 17, page 12, line 27 from the bottom).

- The prior published paper of Coy et al. (Genomics 1996) describes a "transketolase-related gen" with exactly said data bank Accession No. X91817.

- From Mack et al. it is obvious that the term TKTL-1 is not only used by Coy (the discoverer of that gene) but also by the other scientists/members of the relevant technical field.

Should the Examiner require an even more precise definition of "transketolase-like1 gene" he is requested to note claims 69 ("as given in SEQ ID No.1 **and** SEQ ID No. 2") and 70 ("as given in NCIB Accession No. X 91817"). These further recitations makes clear which gene shall be addressed and that this gene is the target of the diagnostic method of the present invention.

In view of the foregoing, reconsideration and withdrawal of all rejections and allowance of the application is respectfully solicited.

If the Examiner believes that a telephone conversation with the Applicant's attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at the telephone number shown below.

The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for any retroactive extensions of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing or during prosecution of this application to Deposit Account No. 16-0877.

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